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Prostatic arterial embolization for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (protocol)

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Prostatic arterial embolization for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of PAE for the treatment of LUTS in men with BPH.

BACKGROUND

Description of the condition

Benign prostatic hyperplasia (BPH) is histologically defined as an increased number of epithelial and stromal cells in the peri-urethral area of the prostate, which may cause prostate enlargement (Roehrborn 2008). Prostate enlargement may constrict urine flow and cause lower urinary tract symptoms (LUTS) (Dunphy 2015). The development of LUTS resulting from BPH is associated with increasing age, and most commonly encountered in men over the

age of 45 years (Barry 1997; Dunphy 2015; Egan 2016). LUTS consist of storage symptoms (such as urinary frequency, urgency, and nocturia) and voiding symptoms (such as urinary hesitancy, weak urinary stream, straining to void, and prolonged voiding). LUTS severity was positively correlated with men's overall distress using patient perception of bladder condition which can be measured by a single-item global question (ranging from 1 (causes no problems at all) to 6 (causes severe problems)) (Chapple 2017). However, LUTS are relatively unspecific and may also be associated with bladder disorders, such as detrusor overactivity. The focus of this review specifically considers the term BPH as pro-

static enlargement with LUTS through which to define the disease condition and potential need for intervention (Dunphy 2015; Roehrborn 2008).

The histological prevalence of BPH is reported to be 8% in the fourth decade of life, and up to 40% and 70% in the sixth and eighth decade of life, respectively (Barry 1995; Roehrborn 2008; Yoo 2012). Aside from LUTS, untreated BPH can result in other serious medical consequences, such as acute urinary retention, urinary tract infection, and upper urinary tract deterioration. Subsequently, BPH results in a negative impact on public health and a reduction in a person's quality of life (Martin 2014; Yoo 2012). BPH results in a significant economic burden as well, with an estimated cost to the USA of USD 4 billion (Taub 2006). It is reasonable to assume that the cost will escalate further in the future with the increasing rise in the male population over 65 years of age (Centers for Disease Control and Prevention 2003).

Treatment decisions in patients with BPH are typically based on the severity of symptoms and subjectively perceived bother, presence of complications, such as acute urinary retention, risk of progression, and treatment-related morbidity. Self-administered questionnaires, namely the International Prostate Symptom Score (IPSS) which consists of eight questions (seven symptom questions + one quality of life question) to evaluate the symptom severity and relative degree of bother, have been used to guide the management of the LUTS (Barry 1995). Watchful waiting and behavioral management are an appropriate first-line option in patients with mild or non-bothersome symptoms. Additional medical treatment options in patients with more bothersome symptoms consist of alpha-blockers, 5-alpha reductase inhibitors or the combination of these two kinds of drugs (EAU 2017; McVary 2011). If conservative and medical treatment fail or BPH-related complications, such as acute urinary retention, recurrent urinary tract infection, bladder stones, hematuria, or renal insufficiency occur, surgical options are considered (EAU 2017; McVary 2011).

There are a wide variety of surgical options for the treatment of BPH, from open simple prostatectomy to minimally invasive surgeries, such as transurethral resection of the prostate (TURP), laser ablation or enucleation of the prostate. According to the current guidelines, TURP remains the "gold standard" surgical procedure for men over 40 years of age who seek professional help for various forms of non-neurogenic benign forms of LUTS. While TURP resulted in a mean decrease in LUTS of 70.0% and a mean increase in maximum flow rate (Q_{max}) by 162%, considerable rates of perioperative and long-term complications, such as bleeding requiring blood transfusion (2%), transurethral resection syndrome (0.8%), acute urinary retention (4.5%), clot retention (4.9%), urinary tract infection (4.1%), bladder neck stenosis (4.7%), urethral stricture (3.8%), retrograde ejaculation (65.4%), and erectile dysfunction (6.5%), have been reported (Ahyai 2010). TURP also commonly requires a period of temporary catheterization, or hospital admission, or both. Reducing treatment-related morbidity and patient burden have therefore motivated the development of

new, minimally invasive alternatives. Minimally invasive surgeries, such as those using electrode, laser, transurethral thermal ablation of prostate (needle ablation, microwave therapy, and radiofrequency ablative techniques), and mechanical stents have been introduced and are widely recognized as alternatives to TURP for some patients (EAU 2017; McVary 2011). Prostatic arterial embolization (PAE) represents a relatively new, minimally invasive treatment option, particularly suitable for men who are at high risk of anesthesia (Wang 2015).

Description of the intervention

Embolization of the prostatic arteries has historically been used to control persistent or massive prostatic bleeding that cannot otherwise be controlled, with typical causes being BPH, locally advanced prostate cancer, or after transurethral prostatectomy (Mitchell 1976). DeMeritt 2000 reported a case of performing PAE with polyvinyl alcohol particles for BPH induced hematuria in which the hematuria immediately stopped and the patient also had symptomatic improvement of his BPH symptoms. They also found that his prostate size was reduced to 52% and 62% of the initial size at five and 12 month follow-up, respectively. Carnevale 2010 reported positive preliminary results of PAE procedures with microspheres as a primary treatment in two patients with acute urinary retention due to BPH. For elderly symptomatic BPH patients, PAE has been introduced as an alternative treatment approach that is performed by a femoral artery puncture using conscious sedation instead of general anesthesia. The procedure is typically performed on an outpatient basis and usually does not require catheterization, unless the patient is in urinary retention beforehand (Wang 2015).

Prior to PAE, preoperative computed tomography or magnetic resonance angiography is typically performed to enable the evaluation of the pelvic artery anatomy. Digital subtraction angiography of the right and left internal iliac arteries is performed to assess the prostatic blood supply (Martins Pisco 2012). Super selective microcatheterization and embolization are then performed on the prostatic arteries. Embolization is typically performed to complete stasis (Carnevale 2010; Martins Pisco 2012; Wang 2015). Cone beam computed tomography can be used to not only help identify all prostatic arteries, but to also identify and avoid the embolization of vessels feeding adjacent pelvic structures (Wang 2015). Particle embolics are almost exclusively used, however, the type and size of particles has varied widely (Carnevale 2010; DeMeritt 2000). The use of vasodilatory medications, once the prostatic artery is catheterized, is also recommended by some authors to avoid premature stasis due to arterial spasm (Martins Pisco 2012).

Adverse effects of the intervention

The major complications of PAE were perineal pain (9.4%), hematuria (9%), and acute urinary retention (7%) (Feng 2017). Acute

urinary retention was the common adverse event in PAE when compared to the control group (9.4% versus 2.0%). The highest prevalence of acute urinary retention was 28.4% amongst the included studies (Wang 2015). Minor complications, such as hematospermia, rectal bleeding, urinary tract infection, inguinal hematoma, and transient urinary frequency were also reported (Feng 2017; Kuang 2017; Pyo 2017; Shim 2017).

How the intervention might work

The underlying mechanism of PAE is the ischemia or hypoxia that induces apoptosis, necrosis, sclerosis, and prostatic shrinkage with cystic transformation of part, or all of the gland, resulting in a softer gland with reduced compression of the urethra (DeMeritt 2000; Sun 2008). In addition, PAE may decrease the plasma concentration of free testosterone that enters prostate cells, thereby lowering the dihydrotestosterone levels in the prostate. This may result in the secondary inhibition of prostate growth (Sun 2008). Furthermore, ischemia or hypoxia may induce prostate cell death and necrosis with a decreased number of some receptors, such as alpha-adrenergic receptors. Therefore, the neuromuscular tone may decrease and result in an improvement in clinical symptoms associated with the dynamic pathologic component of BPH (Zlotta 1997).

Why it is important to do this review

Despite reported relative advantages of PAE, it remains unclear how this procedure compares to the numerous surgical alternatives that exist. While there are existing systematic reviews that compare PAE to other therapies used to treat BPH (Feng 2017; Kuang 2017; Pyo 2017; Shim 2017), none so far has used the same rigorous methodology as Cochrane Reviews, which includes the application of the GRADE approach and its focus on patient-important outcomes (Guyatt 2008). In this era, with the availability of numerous minimally invasive procedures to treat LUTS suggestive of BPH, the findings of this Cochrane Review will be relevant to policymakers, healthcare providers and patients alike.

OBJECTIVES

To assess the effects of PAE for the treatment of LUTS in men with BPH.

METHODS

Criteria for considering studies for this review

Types of studies

We will include parallel group randomized controlled trials (RCTs) and cluster-RCTs. We will exclude cross-over trials, as these study designs are not relevant in this setting. If we only find RCTs that provide low-quality evidence for a given outcome and comparison, we will also include non-RCTs, such as cohort and cross-sectional studies with concurrent comparison groups, as a source of complementary, sequential or replacement evidence for RCTs (Schunemann 2013a). We will not consider including single-armed studies. We will include studies regardless of their publication status or language of publication.

Types of participants

We will define the eligible patient population as men over the age of 40 with a minimum prostate volume of 20 mL or greater (as assessed by ultrasound or cross-sectional imaging), with LUTS as determined by an IPSS of eight or over, and a Qmax of less than 15 mL/sec, as measured by non-invasive uroflowmetry, or invasive pressure flow studies, or both (EAU 2017; McVary 2011). The age limitation is based on the observation that the prevalence of BPH increases in middle-aged and older men, and is infrequent in younger men (Barry 1997; EAU 2017; Egan 2016). We will include studies in which only a subset of participants are relevant to this review, if data are available separately for the relevant subset. We will exclude trials of men with chronic renal failure, untreated bladder calculi or large diverticula, a diagnosis of prostate cancer, urethral stricture disease, and prior prostate, bladder neck, or urethral surgery. We will also exclude studies of patients with other conditions that affect urinary symptoms, such as neurogenic bladder due to spinal cord injury, multiple sclerosis, or central nervous system disease.

Types of interventions

We plan to investigate the following comparisons of experimental intervention versus comparator interventions. Concomitant interventions will have to be the same in the experimental and comparator groups to establish fair comparisons.

Experimental interventions

- PAE

Comparator interventions

- Sham control (or no intervention)
- TURP (monopolar or bipolar)
- Laser ablations of the prostate (e.g. photoselective vaporization of the prostate)
- Laser enucleations of the prostate (e.g. holmium laser enucleation of the prostate)

- Other minimally invasive therapies (e.g. transurethral incision of the prostate, transurethral thermal ablation of the prostate (needle ablation, microwave therapy, and radiofrequency ablative techniques), prostate stent, and prostatic urethral lift)

Comparisons

- PAE versus sham control (or no intervention)
- PAE versus TURP
- PAE versus laser ablations of the prostate
- PAE versus laser enucleations of the prostate
- PAE versus other minimally invasive therapies

Types of outcome measures

We will not use the measurement of the outcomes assessed in this review as an eligibility criterion.

Primary outcomes

- Urologic symptom scores
- Quality of life
- Major adverse events

Secondary outcomes

- Retreatment
- Erectile function
- Ejaculatory function
- Minor adverse events
- Acute urinary retention
- Indwelling urinary catheter
- Hospital stay

Method and timing of outcome measurement

We will use clinically important difference for the review outcomes to rate overall quality of the evidence in the 'Summary of findings' table (Johnston 2010).

Urologic symptom scores

- Mean change measured as a validated scale (such as IPSS).
- We will consider improvement of the IPSS score of three points as a minimal clinically important difference (MCID) to assess efficacy and comparative effectiveness (Barry 1995). If possible, we will use different thresholds of MCID based on the severity of IPSS with a threshold of three for men with mild LUTS, five for moderate LUTS, and eight for severe LUTS (Barry 1995).

Quality of life

- Mean change measured as a validated scale (such as IPSS-quality of life or BPH Impact Index).
- No threshold was established for the IPSS-quality of life. We will use a MCID of one to assess efficacy and comparative effectiveness (Brasure 2016). We will consider improvement of the BPH Impact Index score of 0.5 as a MCID (Barry 1995).

Major adverse events

- For example, postoperative hemorrhage requiring admission or intervention.
- We will use the Clavien-Dindo classification system to assess surgical complications (Dindo 2004), and will categorize grade III, IV and V complications as major. If the study authors of eligible studies did not use the Clavien-Dindo system, we will judge the adverse events by severity using the available information described in the studies.

Retreatment

- Events requiring other surgical treatment modalities (e.g. TURP) within at least six months follow-up due to treatment failure after intervention.

Erectile function

- Mean change, measured as erectile function domain of International Index of Erectile Function (IIEF) or total score of IIEF-5 questionnaire (Rosen 1997).
- We will consider the MCID in the erectile function domain score of IIEF of four (Rosen 2011). If possible, we will use different thresholds of MCID based on the severity of ED, with a threshold of two for men with mild erectile dysfunction, five for moderate erectile dysfunction, and seven for men with severe erectile dysfunction (Rosen 2011). We will also consider improvement of IIEF-5 of over five points as MCID (Spaliviero 2010).

Ejaculatory function

- Mean change, measured as Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD; Rosen 2007).

Minor adverse events

- For example, postoperative fever or pain requiring medication.
- We will use the Clavien-Dindo classification system to assess surgical complications (Dindo 2004), and will categorize grade I and II complications as minor. If the authors did not use

the Clavien-Dindo system, we will grade the adverse events as described above.

Acute urinary retention

- Events requiring catheterization after intervention.

Indwelling urinary catheter

- Measured in days from intervention to urinary catheter removal.

Hospital stay

- Measured in days from admission to discharge.

There is no reported threshold in adverse events, retreatment, ejaculatory function, acute urinary retention, indwelling urinary catheter, and hospital stay. We will consider the clinically important difference for adverse events, retreatment, and acute urinary retention as a relative risk reduction of at least 25% (Guyatt 2011a). We will use a MCID of 25% improvement from baseline in MSHQ-EjD for ejaculatory function (Nickel 2015). We will use a clinically important difference of one day to assess efficacy and comparative effectiveness for indwelling urinary catheter and hospital stay.

We will consider outcomes measured up to and including 12 months after randomization as short-term and later than 12 months as long-term for urologic symptom scores, quality of life, major adverse events, erectile function, ejaculatory function, minor adverse events, and acute urinary retention. We assessed retreatment, indwelling urinary catheter and hospital stay as short-term only.

Main outcomes for 'Summary of findings' table

We will present a 'Summary of findings' table reporting the following outcomes listed according to priority.

1. Urologic symptom scores.
2. Quality of life.
3. Major adverse events.
4. Retreatment.
5. Erectile function.
6. Ejaculatory function.

Search methods for identification of studies

We will perform a comprehensive search, with no restrictions on the language of publication or publication status. We plan to rerun searches within three months prior to anticipated publication of the review.

Electronic searches

We will search the following sources from inception of each database.

- Cochrane Library via Wiley (Appendix 1).
 - *Cochrane Database of Systematic Reviews* (CDSR).
 - Cochrane Central Register of Controlled Trials (CENTRAL).
 - Database of Abstracts of Reviews of Effects (DARE).
 - Health Technology Assessment Database (HTA).
- MEDLINE via Ovid (from 1946; Appendix 2).
- EMBASE via Ovid (from 1974; Appendix 3).
- Scopus (from 1966).
- Web of Science (from 1900).
- Google Scholar.

We will also search the following.

- ClinicalTrials.gov (www.clinicaltrials.gov/).
- World Health Organization (WHO) International Clinical Trials Registry Platform search portal (apps.who.int/trialsearch/).
- Grey literature repository from the current Grey Literature Report (www.greylit.org/).

If we detect additional relevant key words during any of the electronic or other searches, we will modify the electronic search strategies to incorporate these terms and document the changes.

Searching other resources

We will try to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, reviews, meta-analyses and health technology assessment reports. We will also contact study authors of included trials to identify any further studies that we may have missed. We will contact drug/device manufacturers for ongoing or unpublished trials. We will search for unpublished studies by handsearching the abstract proceedings of the annual meetings of the American Urological Association, European Association of Urology, and Radiological Society of North America for the last three years (2015 to 2017).

Data collection and analysis

Selection of studies

We will use reference management software to identify and remove potential duplicate records (EndNote 2016). Two review authors (JHJ, KAM, VN or BR) will independently scan the abstract, title, or both, of remaining records retrieved, to determine which studies should be assessed further through Covidence 2017. Two review authors (JHJ, KAM, VN, or BR) will investigate all potentially relevant records as full text, map records to studies, and classify studies as included studies, excluded studies, studies awaiting classification, or ongoing studies, in accordance with the criteria

for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We will resolve any discrepancies through consensus or recourse to a third review author (PD). If resolution of a disagreement is not possible, we will designate the study as 'awaiting classification' and we will contact study authors for clarification. We will document reasons for exclusion of studies that may have reasonably been expected to be included in the review in a 'Characteristics of excluded studies' table. We will present an adapted PRISMA flow diagram showing the process of study selection (Liberati 2009).

Data extraction and management

We will develop a dedicated data abstraction form that we will pilot test ahead of time.

For studies that fulfil inclusion criteria, two review authors (JHJ, KAM, VN, or BR) will independently abstract the following information, which we will provide in the 'Characteristics of included studies' table.

- Study design.
- Study dates (if dates are not available then this will be reported as such).
- Study settings and country.
- Participant inclusion and exclusion criteria (e.g. age, baseline IPSS).
- Participant details, baseline demographics (e.g. age, prostate size, IPSS, American Society of Anesthesiologists physical status classification system, radiation dose for PAE).
- The number of participants by study and by study arm.
- Details of relevant experimental and comparator interventions, such as embolization catheterization approach (unilateral or bilateral) and characteristics of the embolization agent used (e.g. polyvinyl alcohol particle size).
- Definitions of relevant outcomes, and method (e.g. type of instrument, such as IPSS) and timing of outcome measurement (e.g. in months) as well as any relevant subgroups (e.g. based on age, prostate volume, severity of LUTS).
- Study funding sources.
- Declarations of interest by primary investigators.

We will extract outcome data relevant to this Cochrane Review as needed for calculation of summary statistics and measures of variance. For dichotomous outcomes, we will attempt to obtain numbers of events and totals for population of a 2x2 table, as well as summary statistics with corresponding measures of variance. For continuous outcomes, we will attempt to obtain means and standard deviations or data necessary to calculate this information. We will resolve any disagreements by discussion, or, if required, by consultation with a third review author (PD).

We will provide information, including trial identifier, about potentially relevant ongoing studies in the table 'Characteristics of ongoing studies'.

We will attempt to contact authors of included studies to obtain key missing data as needed.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary study, we will maximize yield of information by mapping all publications to unique studies and collating all available data. We will use the most complete data set aggregated across all known publications. In case of doubt, we will give priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Two review authors (JHJ, KAM, VN, or BR) will assess the risk of bias of each included study independently. We will resolve disagreements by consensus, or by consultation with a third review author (PD). We will present a 'Risk of bias' summary figure to illustrate these findings. We will further summarize the risk of bias across domains for each outcome in each included study, as well as across studies and domains for each outcome in accordance with the approach for summary assessments of the risk of bias presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b; Sterne 2016). We will not combine risk of bias from RCTs with that from non-RCTs due to inherently different biases between each study design (Reeves 2011).

Assessment of risk of bias in RCTs

We will assess risk of bias using Cochrane's 'Risk of bias' assessment tool (Higgins 2011b). We will assess the following domains.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other sources of bias.

We will judge risk of bias domains as 'low risk', 'high risk' or 'unclear risk' and will evaluate individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

For selection bias (random sequence generation and allocation concealment), we will evaluate risk of bias at a trial level.

For performance bias (blinding of participants and personnel), we will consider all outcomes similarly susceptible to performance bias.

For detection bias (blinding of outcome assessment), we will group outcomes as susceptible to detection bias (subjective outcomes) or not susceptible to detection bias (objective outcomes).

We define the following endpoints as subjective outcomes.

- Urologic symptom scores.
- Quality of life.
- Major adverse events.
- Erectile function.
- Ejaculatory function.
- Minor adverse events.

We define the following endpoints as objective outcomes.

- Retreatment.
- Acute urinary retention.
- Indwelling urinary catheter.
- Hospital stay.

We will assess attrition bias (incomplete outcome data) on a per outcome basis, but will seek to create groups of outcomes based on similar reporting characteristics.

For reporting bias (selective reporting), we will evaluate risk of bias at a trial level.

We will further summarize the risk of bias across domains for each outcome in each included study, as well as across studies and domains for each outcome, in accordance with the approach for summary assessments of the risk of bias presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

Assessment of risk of bias in non-RCTs

We will assess risk of bias in non-RCTs with ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions (Sterne 2016). We will assess the following domains.

- Bias due to confounding.
- Bias in selection of participants into the study.
- Bias in classification of interventions.
- Bias due to deviations from intended interventions.
- Bias due to missing data.
- Bias in measurement of outcomes.
- Bias in selection of the reported result.

We will judge risk of bias domains as 'low risk', 'moderate risk', 'serious risk', 'critical risk', or 'no information' and will evaluate individual bias items as described in Sterne 2016.

Measures of treatment effect

We will express dichotomous data as risk ratios with 95% confidence intervals (CIs). We will express continuous data as mean differences (MDs) with 95% CIs unless different studies use different measures to assess the same outcome, in which case we will express data as standardized MDs with 95% CIs.

Unit of analysis issues

The unit of analysis will be the individual participant. Should we identify cluster-randomized trials, or trials with more than two intervention groups for inclusion in the review, we will handle these

in accordance with guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c).

Dealing with missing data

We will obtain missing data from study authors, if feasible, and will perform intention-to-treat analyses if data are available; we will otherwise perform available case analyses. We will investigate attrition rates, e.g. dropouts, losses to follow-up and withdrawals, and will critically appraise issues of missing data. We will not impute missing data.

Assessment of heterogeneity

In the event of excessive heterogeneity, unexplained by subgroup analyses, we will not report outcome results as the pooled effect estimate in a meta-analysis, but will provide a narrative description of the results of each study.

We will identify heterogeneity (inconsistency) through visual inspection of the forest plots to assess the amount of overlap of CIs, and the I^2 statistic, which quantifies inconsistency across studies to assess the impact of heterogeneity in the meta-analysis (Higgins 2002; Higgins 2003); we will interpret the I^2 statistic as follows (Deeks 2011).

- 0% to 40%: may not be important.
- 30% to 60%: may indicate moderate heterogeneity.
- 50% to 90%: may indicate substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

When we find heterogeneity, we will attempt to determine possible reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

We will attempt to obtain study protocols to assess for selective outcome reporting.

If we include 10 studies or more investigating a particular outcome, we will use funnel plots to assess small study effects. Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials) and publication bias. We will therefore interpret results carefully.

Data synthesis

Unless there is good evidence for homogeneous effects across studies, we will summarize data using a random-effects model. We will interpret random-effects meta-analyses with due consideration of the whole distribution of effects. In addition, we will perform statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). For dichotomous outcomes, we will use

the Mantel-Haenszel method; for continuous outcomes, we will use the inverse variance method. We will use Review Manager 5 software to perform analyses (Review Manager 2014). We will analyze the results for RCTs and non-RCTs separately (Reeves 2011).

Subgroup analysis and investigation of heterogeneity

We expect the following characteristics to introduce clinical heterogeneity, and plan to carry out subgroup analyses with investigation of interactions.

- Patient age (less than 65 years versus greater than or equal to 65 years).
- Prostate volume (less than or equal to 40 mL versus greater than 40 mL).
- Severity of LUTS based on IPSS (score less than or equal to 19 (moderately symptomatic) versus greater than 19 (severely symptomatic)).

These subgroup analyses are based on the following observations.

- Age is a well-known risk factor of BPH surgery. Elderly patients have a higher rate of postoperative complications compared with younger patients (Bhojani 2014; Pariser 2015). The age cut-off is based on the WHO definition of old age (WHO 2002).
- The outcomes and complications of ablative procedures, such as TURP correlate with prostate volume (Reich 2008). The prostate volume cut-off > 40 cc is based on this being the most commonly used threshold to distinguish 'small' from 'large' for the indication of treatment with a 5-alpha reductase inhibitor (EAU 2017).
- The relationship between changes in IPSS scores and patient global ratings of improvement is influenced by the baseline scores (Barry 1995).

We plan to perform subgroup analyses limited to the primary outcomes. We will use the test for subgroup differences in Review Manager 2014 to compare subgroup analyses if there are sufficient studies.

Sensitivity analysis

We plan to perform sensitivity analyses limited to the primary outcomes in order to explore the influence of the following factor (when applicable) on effect sizes.

- Restricting the analysis by taking into account risk of bias, by excluding studies at 'high risk' or 'unclear risk'.

'Summary of findings' table

We will present the overall quality of the evidence for each outcome according to the GRADE approach, which takes into account five criteria not only related to internal validity (risk of bias, inconsistency, imprecision, and publication bias), but also to external validity, such as directness of results (Guyatt 2008). For each comparison, two review authors (JHJ, KAM, VN, or BR) will independently rate the quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very low' using GRADEpro GDT 2015. We will resolve any discrepancies by consensus, or, if needed, by arbitration by a third review author (PD). For each comparison, we will present a summary of the evidence for the main outcomes in a 'Summary of findings' table, which provides key information about the best estimate of the magnitude of the effect in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in effect estimates for each outcome (Guyatt 2011b; Schünemann 2011b). If meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table.

For RCTs, we will take into account five criteria not only related to internal validity (risk of bias, inconsistency, imprecision, and publication bias), but also to external validity, such as directness of results for downgrading the quality of evidence for a specific outcome (Schünemann 2011c). For non-RCTs, we will take into account three criteria for upgrading the quality of evidence (large magnitude of effects, all plausible confounding that would reduce a demonstrated effect or suggest a spurious effect when results show no effect, and dose-response gradient) (Schünemann 2011c).

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* Indicates the major publication for the study

APPENDICES

Appendix I. Cochrane Library search strategy

1	MeSH descriptor: [Prostatic Hyperplasia] explode all trees
2	(hyperplasia near/3 prostat*):ti,ab,kw (Word variations have been searched)
3	hyperplasia of the prostate:ti,ab,kw (Word variations have been searched)
4	prostatic hyperplasia:ti,ab,kw (Word variations have been searched)
5	(hypertrophy near/3 prostat*):ti,ab,kw (Word variations have been searched)
6	(adenoma* near/3 prostat*):ti,ab,kw (Word variations have been searched)
7	MeSH descriptor: [Lower Urinary Tract Symptoms] explode all trees
8	lower urinary tract or "luts":ti,ab,kw (Word variations have been searched)
9	prostatism:ti,ab,kw (Word variations have been searched)
10	MeSH descriptor: [Prostatism] explode all trees
11	MeSH descriptor: [Urinary Bladder Neck Obstruction] explode all trees
12	bladder outlet obstruction:ti,ab,kw (Word variations have been searched)
13	(prostat* near/3 enlarg*):ti,ab,kw (Word variations have been searched)
14	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13
15	MeSH descriptor: [Embolization, Therapeutic] explode all trees
16	emboli?ation*:ti,ab,kw (Word variations have been searched)
17	15 OR 16
18	14 AND 17

Appendix 2. MEDLINE (via Ovid) search strategy

1	exp Prostatic Hyperplasia/
2	Prostat* adj3 hyperplasia.tw.
3	Prostat* adj3 adenoma.tw.
4	Prostat* adj3 hypertrophy.tw.
5	(BPH or BPO or BPE).tw.
6	exp Lower Urinary Tract Symptoms/
7	lower urinary tract.tw.
8	LUTS.tw.
9	exp Prostatism/
10	Prostatism.tw.
11	exp Urinary Bladder Neck Obstruction/
12	(Bladder* adj3 obstruct*).tw.
13	BOO.tw.
14	1-13 OR
15	exp Embolization, Therapeutic/
16	emboli#ation\$.tw.
17	15-16 OR
18	14 AND 17
19	(animals not (humans and animals)).sh.
20	18 not 19

Appendix 3. EMBASE (via Ovid) search strategy

1	prostate hypertrophy'/exp
2	hyper* NEAR/3 prostat*):ab,ti
3	(adenoma* NEAR/3 prostat*):ab,ti
4	BPH' OR 'BPO' OR 'BPE':ab,ti
5	lower urinary tract symptom'/exp
6	lower urinary tract' OR 'LUTS':ab,ti
7	prostatism':ab,ti
8	prostatism'/exp
9	bladder obstruction'/exp
10	(bladder* NEAR/3 obstruct*) OR 'BOO':ab,ti
11	(prostat* NEAR/3 (enlarg* OR obstruct*)):ab,ti
12	((urinary or urethra* or urination or LUT*) NEAR/3 (symptom* or complain*)):ab,ti
13	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12
14	'artificial embolization'/exp
15	embolisation*:ab,ti
16	embolization*:ab,ti
17	14 OR 15
18	13 AND 16
19	('animals'/exp) NOT ('humans'/exp and 'animals'/exp)
20	17 not 18

CONTRIBUTIONS OF AUTHORS

Jae Hung Jung (JHJ): conceived, designed, and wrote the protocol.

Tae Young Shin (TYS): wrote the protocol, provided clinical guidance.

Karen Ann McCutcheon (KAM): wrote the protocol, provided clinical guidance and critical content.

Michael Borofsky (MB): wrote the protocol, provided clinical advice and critical content.

Vikram Narayan (VN): provided clinical advice and critical content.

Shamar Young (SY): provided clinical advice and critical content.

Jafar Golzarian (JG): provided clinical advice and critical content.

Myung Ha Kim (MHK): created search strategies and searched for trials.

Balaji Reddy (BR): provided clinical advice.

Philipp Dahm (PD): conceived, designed and wrote the protocol, reviewed critical content, and gave final approval.

DECLARATIONS OF INTEREST

JHJ: none known.

TYS: none known.

KAM: none known.

MB: none known.

VN: none known.

SY: none known.

JG: none known.

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External sources

- No sources of support supplied

NOTES

We have based parts of the Methods section of this protocol on a standard template developed by the Cochrane Metabolic and Endocrine Disorders Group, which has been modified and adapted for use by Cochrane Urology.